REMARKS

The issues outstanding in the Office Action mailed January 16, 2009, are the requirement for restriction and the rejections under 35 U.S.C. 112 and 103. Reconsideration of these issues, in view of the following discussion, is respectfully requested.

Requirement for Restriction

Applicants traversal of the requirement for restriction, inasmuch as it separates the method of use claims from the compound claims, is maintained. The Office Action, at page 2, quotes rule 13.2, but does not take into account Appendix B to the PCT rules explaining rule 13.2. For example, section (e), entitled "combinations of different categories of claims" states that the method for determining unity of invention under rule 13.2 "shall" be considered as permitting, in particular, the inclusion of any one of the following combinations of claims of different categories in the same international application (i) in addition to an independent claims for a given product, an independent claim for a process especially adapted from the manufacture of a said product, and an independent claim for the use of the said product. It is not seen that, in this situation, a requirement of a special technical feature is required.

In any event, inasmuch as the present claims are allowable, in view of the following discussion, it is submitted that the method of use claim which remains should be rejoined for examination, in accordance with MPEP 821.04.

Rejections Under 35 U.S.C. 112

Claims 11, 12 and 13 have been rejected under 35 U.S.C. 112, second paragraph. It is submitted that, in order to streamline prosecution and for commercial reasons, claim 13 has been canceled, with the independent compound claim now being claim 14. Thus, this rejection is moot. Withdrawal thereof is respectfully requested.

Claims 1-14 and 16 have been rejected under 35 U.S.C. 112, first paragraph. It is argued, at page 7 of the Office Action, that various compounds within the scope of the claims are not enabled. In particular, this rejection also argues that amine oxides in geometrical isomers are not

enabled. Applicants respectfully disagree. First, with respect to the discussion spanning pages 9-21 of the Office Action, in view of the fact that it is claim 14, directed to specific compounds whose specific synthesis is taught in the present application, it is submitted that this portion of the rejection is moot. Thus, the only relevant portion of the rejection is that spanning pages 22-24, concerning preparation of hydrates, and the portion of the prior rejection directed to amine oxides and various isomers. With respect to amine oxides, amine oxide salts are well known and conventional. See, for example, EP 0756592 (attached). With respect to solvates and hydrates, it is argued that the recitation of "hydrates" in the claims is no different than previously canceled solvates. Regardless, the preparation of such solvates is well known and highly conventional. For example, *Vippagunta* on page 15, top of first column, states that

> It has been established that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. (Emphasis added.)

Likewise, the abstract of *Vippagunta* starts with the statement that

> Many drugs exist in the crystalline solid state due to reasons of stability and ease of handling … Crystalline solids can exist in the form of polymorphs, solvates or hydrates. (Emphasis added.)

Also on page 4, first paragraph, *Vippagunta* states that

> Most organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms. …
>
> The common crystalline forms found for a given drug substance are polymorphs and solvates. (Emphasis added.)

Moreover, *Vippagunta* throughout the reference teaches various solvates, hydrates, etc., structural aspects thereof, examples thereof, including preparation techniques, and methods/techniques for the characterization thereof. See, e.g., pages 15-18.

While it may be true, that the prediction of what a particular solvate of a compound will actually look like, e.g., whether one, 3 ½, 6 or 12 solvent molecules are incorporated, the Office Action is incorrect with respect to the alleged lack of enablement.

One of ordinary skill in the art in the field of pharmaceuticals would know how to proceed in preparing solvates and how such solvates would be identified or characterized, e.g., by

polarized light microscopy, etc. See extensive list of techniques identified on column 2 of page 18.

Additionally, based on the above discussed statistics in this field provided by *Vippagunta*, one of ordinary skill in the art would also have a good expectation for success. While certain predictions may be difficult in the art of forming solvates, the formation of solvates is common with pharmaceutically active ingredients and methods of detecting and characterizing them are well-known and widely applied routinely.

In sum, *Vippagunta*, clearly shows that there is no lack of enablement.

Thus, the Office Action has not carried its burden in establishing a lack of enablement because the Office Action has not established any basis to doubt objective enablement. See *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (1971) holding that a specification disclosure which "contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is *reason to doubt the objective truth* of the statements contained therein which must be relied on for enabling support." (Emphasis added.) See also *In re Bundy*, 209 USPQ 48 (1981) holding that the "PTO must have adequate support for its challenge to the credibility of applicant's statements of utility," which statements were made in *Bundy* in the context of an enablement rejection, and which is lacking in the present case. In view of the state of the art, it is evident that there is no indication that one of ordinary skill in the art would have questioned that solvates could be formed. *Rasmussen v. Smithkline Beecham Co.*, 75 USPQ2d 1297 (CA FC 2005).

Nevertheless, applicants provide further information clearly demonstrating that solvate formation is a common phenomenon among pharmaceutical substances, i.e., Polymorphism: in the pharmaceutical industry (edited by *Ralf Hilfiker*; 2006 Wiley-VCH), Chapter 8, The Importance of Solvates, by *U. J. Griesser*, pp. 211-222 (hereinafter *Griesser*).

On page 220, *Griesser* teaches that

> Over almost two decades we carefully collected data on the solid-state properties of a few thousand pharmaceutically relevant organic compounds, with special focus on those drug substances

> listed in the Pharmacopoeia European (PhEur). The 1997 edition of PhEur contained 559 well-defined organic drug compounds. … For more than 55% of them either polymorphs or solvates are known. In a newer evaluation of a larger set of data (PhEur edition 4.02, 8008 solid organic compounds … this fraction increased only slightly to 57%. As shown in Fig. 8.4, 29% of the compounds are known to form hydrates, 10% other solvates … (Emphasis added.)

Additionally, various factors in considering whether solvates would be expected to form are identified by *Griesser* on pages 220-221, e.g., salt forms, molecular size, lipophilicity. A citation is provided for ascertaining "further trends and interrelations between molecular properties and solvate/hydrate formation." See the middle of page 221. All this demonstrates that one of ordinary skill in the art would know or have guidance as to what factors to consider in expectation of success.

Moreover, under the section titled "Generation and Characterization of Solvates" on page 222, *Griesser* teaches that

> Since it is imperative to establish the crystal forms of an active pharmaceutical ingredient (API) to satisfy the regulatory authorities …, solvates of drug compounds are now preferentially discovered in systematic polymorph screenings. … **Automated crystallization systems and strategies** have been developed to speed up this process, **allowing thousands of crystallization experiments in a short time**. (Emphasis added.)

In view of the state of the art of solvate formation, e.g., solvate formation being a very common phenomenon associated with drug substances, the generation and examination of which is done with highly automated machines, the Office Action has not established that it would require undue experimentation by one of ordinary skill in the art to prepare and even characterize the solvates of a compound.

While the amount of work to prepare solvates of the compounds of the invention may require some effort or maybe even considerable effort (although not admitted), no undue experimentation is required in the preparation of solvates. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from disclosures in the patent coupled with information known in the art without undue experimentation." *United States v.*

Telectronics, 857 F.2d 778, USPQ 2d 1217 (Fed. Cir. 1988). One of ordinary skill in the art merely through routine laboratory efforts can take various compounds of the invention, which are explicitly admitted by the Office Action to be enabled at the top of page 3, bring them together with various solvents and check whether solvates have formed. This type of work is merely routine laboratory work and does not require undue experimentation. Moreover, as discussed in *In re Wands*, cited in the Office Action, the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine," which it is in the present case.

Reconsideration is respectfully requested. Accordingly, withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. 103

Claim 14 has not been subjected to the rejection under 35 U.S.C. 103. Accordingly, it is submitted that the claims are in condition for allowance, and passage to issue is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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